REMARKS

This amendment is filed in response to the Non-Final Office Action dated February 19, 2009 wherein all pending claims 84-95 stand rejected.

Status of the Claims and Claim Support for Amendments

Claim 84 is canceled.

Claim 96 is added.

Claims 85-96 are pending.

Claims 85, 87 and 91 are amended.

Amendment of claim 84 is in response to the 35 USC 112 rejection.

Amendment of claim 87 is supported in [0149] and in response to rejections under 35 USC 112.

Amendment of claim 91 is in response tot rejections under 35 USC 112 and is supported in [0177].

The new claim 96 is redrafted to a process claim as required by the Examiner. Yields of increase in S-GAG and DNA production(determined as DNA index) are supported in Table 2 and [0229] for DNA index and in Table 2 and [0228] for production of S-GAG.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 84-95 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Support is not found in the specification for at least 50% more S-GAG and at least 49% more DNA than a control as required in the last two lines of claim 84. Support is not found in lines 6-12 of paragraph 0228 and Table 2.

Applicants disagree. Par [228], lines 10-12 clearly states that the S-GAG production increased to 152% for a group treated with a cyclic hydrostatic pressure and to 162% when treated with a constant hydrostatic pressure compared to controls. That is more than 50% increase in S-GAG production. Situation is similar with DNA where the DNA index, measured by the Hoechst Dye DNA assay rose from 1 to 1.49. That is 49% of increase. However, to meet Examiner's rejections, Applicants amended claim 84 to recite verbatim the language used in [228].

With this amendment, the rejection is overcome and should be withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 84-95 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Examiner argues that Claim 83 is confusing and unclear by being product-by-process by defining the claimed implantable construct in terms of process steps and conditions of how the construct is produced, and not setting forth clear, distinct and positive process steps in the order they are carried out such that there is a clear relationship between the steps, and each step has clear antecedent basis in a previous step. A product-by-process claim must set forth process steps as would be recited in a process of making the product. See MPEP 2113 and 2173.05(P) as to the proper form of a product-by-process claim.

Applicants note that Claim 83 is not in the application. Therefore, it is presumed that Examiner meant claim 84.

Examiner argues that the prior amendment urges the new claims are not product-by-process. However, claim 84 is clearly requiring process limitations for producing the construct.

Applicants disagree. However, to advance the prosecution, Claim 84 was replaced with a new product-by-process claim 96 wherein all issues raised by the Examiner are taken in consideration.

Examiner argues that Claims 84 and 85 are unclear as to how constant hydrostatic pressure can have a frequency as required of "Hz".

Claim 94 is reworded to clarify this issue.

Examiner argues that Claims 84 and 91 are unclear as to structure that is a "tissue processor", and in claim 91 structure that is a "Tissue Engineering Support System". Structure that is within and not within the scope of these limitations is uncertain.

Applicants disagree. Tissue processor is described in a great detail in [0177] with Tissue engineering Support System (TESS) being actually illustrated in Figure 2B. The TESS is described in the US patent 6,432,713, incorporated by reference. It is Applicants position that the description in the specification provides enough information to determine what is the scope of limitations for these two structures.

Examiner argues that in Claim 84, requiring synthesizing extracellular matrix, S-GAG and DNA is confusing as to whether these are separate components or are components that form the extracellular matrix formed. The claim is unclear whether the components are synthesized inside the chondrocytes or exterior to the chondrocytes.

Applicants disagree. Paragraph [208] discloses that increased cell proliferation shows the activation of the previously inactive cells. Increased level of DNA shows genetic activation of inactive chondrocytes. Increased production of Type II collagen and S-GAG shows that the production of the extracellular matrix has been activated by the activation process.

Examiner argues that in the last line, claim 84 is unclear how the control of non-activated chondrocytes is produced.

Examiner's point for use of a term "control" of non-activated chondrocytes is well taken. This description is no

longer used in the new claim 96. For Examiner's information it referred to chondrocytes not treated (activated) that were used as a control group for determination of increase of S-GAG or DNA production.

Examiner argues that in claim 87, "honeycomb-like" is uncertain as to meaning and scope. Being like a honeycomb is relative and subjective.

Applicants disagree. There is a description of honeycomb-like lattice in the [0149] and [0158]-[0161] However, to make the description more definitive, Applicants amended claim 87 to include more detailed description and eliminating the term "like".

With these amendments, it is believed that all rejections under 35 USC 112 are overcome.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 84-95 are rejected under 35 U.S.C. 102(a) as being anticipated by Smith et al (6,528,052).

Examiner argues that the claims are drawn to a hyaline cartilage construct comprising a collagenous porous support matrix having pores between 100 and 300 μm seeded with chondrocytes activated in a tissue processor under conditions of

cyclic or constant hydrostatic pressure so the chondrocytes synthesize an extracellular matrix, S-GAG and DNA, and at least 50% more of S-GAG and at least 49% more of DNA is synthesized than a control. Activation involves applying a cyclic or constant hydrostatic pressure from about 0.5 to 5 MPa above atmospheric pressure at a frequency of from about 0.01 to 2 Hz for about one hour to 30 days followed by a resting period from about one day to sixty days, under perfusion with a perfusion medium at a flow rate from about 1 to 500 uL per minute under an oxygen concentration of 1-20%.

Examiner further argues that Smith et al disclose repair and regeneration of cartilage by a process that involves in vivo, ex vivo or in vitro treatment of cartilage or cartilage cells (chondrocytes) in a support such as a scaffold or collagen matrix (col 6, lines 14-16) by using a loading regiment involving conditions of intermittent application of periods of hydrostatic pressure followed by periods of recovery in situ (col 4, lines 25-31, and col 7, line 30 to col 8, line 8). The recovery period can be at atmospheric or low constant pressure (col 7, lines 48-50). In vitro treatment is performed by obtaining cartilage cells from cartilage, and applying the loading regiment conditions while culturing the cartilage cells in suspension within a scaffold/support, and implanting the resultant tissue or cells into a patient (col 9, lines 23-30, and col 11, lines 5-9). Articular chondrocytes (col 16, line 65) are isolated from cartilage using enzyme digestion (col 17, line 4). The chondrocytes can be autologous or not autologous (col 9, line 33). Articular cartilage can be regenerated and repaired (col 1, lines 41-43).

Examiner maintains that a cartilage construct produced by the process of Smith et al is the same the construct presently claimed for implantation into a cartilage lesion or defect. No difference is seen in the presently claimed process from the process of Smith et al that would result in a materially different construct. Examiner concludes that the process of Smith et al will inherently produce a construct containing extracellular matrix, S-GAG and DNA as claimed.

Applicants disagree and respectfully submit that there is no anticipation of the instant claims by Smith et al and that the instant construct is not the same, inherently or not, as the one that would be produced by Smith et al.

The instant claims are directed to an implantable construct prepared by a process comprising steps of: preparing a collagenous support matrix (**disclosed by Smith**), having pores limited to 100-300 μm, important aspect for infiltration of chondrocytes, growth and propagation of cells within the construct (**NOT disclosed by Smith**), seeding isolated chondrocytes in a collagen support matrix (**disclosed by Smith**), subjecting said matrix seeded with said chondrocytes to activation (**NOT disclosed by Smith)** to an active stage wherein said activated chondrocytes divide, multiply and promote growth of an extracellular matrix (**NOT disclosed by Smith)**, said activation performed in a tissue processor (**NOT disclosed by Smith, Smith discloses a use of apparatus for intermittent hydrostatic loading**) and comprising treating said matrix seeded with said chondrocytes to a cyclic or constant hydrostatic pressure between about 0.5 MPA and 5 MPA above atmospheric pressure (**disclosed by Smith**), wherein for the cyclic hydrostatic pressure, such

pressure is applied at a frequency between 0.01 Hz and 2.0 Hz (**disclosed by Smith**), wherein the cyclic or static hydrostatic pressure is applied for about 1 hour to about 30 days (**NOT disclosed by Smith**), followed by a resting period of about 1 day to about 60 days (**NOT disclosed by Smith, Smith discloses recovery period 4-100 days**), under perfusion (**NOT disclosed by Smith**), with a perfusion medium at a rate of perfusion flow between 1 µL and 500 µL/minute (**NOT disclosed by Smith**), and under oxygen concentration between 1% and 20% (**NOT disclosed by Smith**), wherein the tissue processor comprises at least a pressure generator for applying a constant or cyclic hydrostatic pressure (**disclosed by Smith)**, and wherein following the activation regimen, the activated chondrocytes are dividing (**NOT disclosed by Smith**), multiplying (**NOT disclosed by Smith**), growing the extracellular matrix (**NOT disclosed by Smith**) and proliferating (**NOT disclosed by Smith**) and producing sulfated glycosaminoglycan (S-GAG) and DNA, wherein production of S-GAG by said activated chondrocytes is increased to at least 152% compared to chondrocytes not subjected to said activation (**NOT disclosed by Smith**) and wherein a DNA content index, determined by Hoechst Dye DNA assay, is increased by said activated chondrocytes to the DNA content index 1.49 compared to that of the DNA content index 1 observed in chondrocytes not subjected to said activation (**NOT disclosed by Smith**).

It is Applicants' contention that the construct, produced by activation of chondrocytes and containing high level of extracellular matrix macromolecules produced due to a complex conditions to which are the chondrocytes subjected as a whole, is not produced by Smith reference.

The activated chondrocytes in an active stage where they divide, multiply and promote growth of the extracellular matrix by accumulating extracellular macromolecules, such as sulfated glycosaminoglycan (S-GAG)[0234], and DNA, to the extent that is the subject matter claimed herein, are nowhere disclosed in Smith.

Smith discloses a method for repair of damaged, injured or aged articulate cartilage. Smith further discloses that using his method, the levels of aggrecan and Type II collagen were able to be restored to physiological levels of 4-7%, wet wt, of aggrecan from those of 0.1-1%, wet wt, of aggrecan observed during pathological conditions, and to 10-29%, wet wt, regenerated levels of Type II collagen from 1-10%, wet wt, of Type II collagen observed during pathological conditions, such as when the cartilage was damaged, injured or aged. As described in Smith, column 8, lines 52-62, functionality testing determined that by using Smith regimen, the damaged, injured or aged cartilage was able to be restored to its pre-damaged, pre-injured or pre-aged physiological conditions.

Nowhere Smith discloses that there is a construct that would contain chondrocytes able to synthesize at least 152% of S-GAG compared to chondrocytes not subjected to said activation and wherein a DNA index, determined by Hoechst Dye DNA assay, is increased to 1.49 compared to that of index 1 observed in chondrocytes not subjected to a process of the invention including all conditions used for the chondrocyte activation.

Examiner continues to argue that the conditions utilized in the instant process and claimed herein are not different and more specific then those disclosed by Smith. Applicants respectfully

disagree. The instant process includes processing conditions, not disclosed anywhere in the prior art or by Smith, that prove to be important factors in substantially increased production of extracellular macromolecules and thereby important for cell activation according to the invention. These conditions are predetermined before the chondrocytes activation begins and are as stated in the claim 96 and in dependent claims 85-95.

Applicants reiterate that Smith does not provide conditions for processing of the seeded support matrix in the tissue processor under constant perfusion flow and under oxygen or carbon dioxide atmosphere that are responsible for much higher yields of, for example, S-GAG production.

Moreover, these conditions permit regulation of S-GAG and DNA production and thereby also regulate production of the extracellular matrix and cell proliferation. For example when the flow rate of the medium is reduced to 0.005 mL/min, under otherwise the same conditions of the pressure, incubation time and number of days in culture, such reduction results in approximately 36% increase in S-GAG production from 78.75 to 107.33 µg/cell construct (see Table 3 and [0239]). When the lower perfusion rate is used vis-a-vis DNA production, the lower perfusion rate results in a higher DNA content index used as a measure for determination of cell proliferation. When the higher perfusion rate was used, the DNA content index decreased from 1.5 to 1.2 resulting in smaller cell proliferation [0238]. Similarly, the oxygen concentration plays a role in increased S-GAG production from 60.89 to 105.59 µg/cell construct when the oxygen concentration is reduced from 20% (normal atmospheric levels of oxygen) to only 2% (see Table 4 and [0248]).

Conditions that Examiner dismisses as not being important for distinguishing the invention from that of Smith reference, account for increased levels of production of S-GAG and thereby increased production of extracellular matter and for increased levels of DNA content index resulting in increased cell proliferation. Only due to the instant process, the cell proliferation can be increased or decreased and the production of S-GAG can be regulated. Therefore, the instant invention, i.e., the construct fabricated under the preset set of conditions according to the invention process, results in substantially increased production of S-GAG and DNA by more them 50% (152%) and 49% (DNA index increase to 1.49), respectively. The yield that can be manipulated and particularly such high yields as disclosed herein are nowhere disclosed in Smith et al.

Anticipation requires that the anticipatory and instant inventions are the same, that is that the construct, or the process for its production are the same, as well as that the construct of the prior art and the construct of the invention functions in the substantially the same way. Quite clearly that is not so. Smith does not use controlled conditions, oxygen, carbon dioxide atmosphere, perfusion rate, loading density or tissue processor that were shown to be instrumental in the functioning construct of the invention able to synthesize high amounts of proteins important for production of implantable construct containing chondrocytes activated according to the instant invention.

It is submitted that the invention is not anticipated by Smith et al and the rejections should be withdrawn. It is

respectfully requested that Examiner withdraws the rejections under 35 USC 102 over Smith.

Claim Rejections - 35 USC § 103

Examiner further rejects claims 84-95 are under 35 U.S.C. 103(a) as being unpatentable over Smith et al (6,528,052) in view of Lee et al (6,306,169) and Burg (6,991,652), and if necessary in further view of Atkinson et al (6,511,958).

The invention and Smith et al are described above.

Examiner submits that Lee et al disclose producing an implant containing cells such as chondrocytes (col 7, line 8) by isolating the cells from tissue, proliferating the cells in a medium containing serum to obtain a sufficient number of cells, and seeding the cells in a construct (col 7, lines 13-17) such as a collagen sponge (col 12, line 17). A collagen sponge can be infiltrated with an alginate or agarose solution containing the cells, and the alginate or agarose gelled within the sponge (col 13, lines 11-25). This procedure produces a construct having mechanical function that resembles that processed by tissue to be repaired (col 4, lines 28-37).

Examiner further argues that Burg discloses forming a hydrogel-cell composition for use in forming new tissue such as cartilage. Before the cell are incorporated in a construct, the cells can be expanded in number by culturing in vitro in a medium containing serum (col 7, lines 20-29). Temperature-dependent hydrogels can be used (paragraph bridging cols 5 and 6). The hydrogels have reverse gelation properties, and are liquids at or below room temperature, and gel when warmed to higher temperatures, e.g. body temperature.

Examiner maintains that when incorporating chondrocytes from cartilage into a scaffold for treatment as disclosed by Smith et al, it would have been obvious to expand the number of cells by in vitro culturing in a culture medium prior to incorporating the cells in the scaffold as suggested by Lee et al and Burg expanding the number of cells before incorporating the cells in a scaffold for implanting.

According to Examiner, the resultant construct will be a cartilage construct as presently claimed. Smith et al disclose using a hydrostatic pressure and frequency of applying the pressure that are the same or substantially the same as used in the present claims. Perfusion with a medium as claimed during treatment with hydrostatic pressure would have been obvious to provide nutrients for the cells to maintain the cells active for growth. The conditions of dependent claims are suggested by conditions used by the references. Air contains slightly above 20% oxygen and using slightly less than 20% oxygen would have been an obvious variation that would not be expected to produce a difference in result. Smith et al disclose 7.5% carbon dioxide (col 17, line 10), and using 5% as in claim 94 is an obvious variation that would not be expected to produce a difference in result. Atkinson et al further disclose repairing cartilage lesions, and if needed would have further suggested conditions that can be used.

Applicants disagree. As already described above in arguments presented in 102 rejections, Smith et al may have utilized some but definitely not all of the conditions in treatment of damaged, injured or aged cartilage and was able to restore such cartilage from the pathological conditions to physiological conditions.

However, he produces no construct that would be equal to that, that would function in the same way or even similarly, or of which production would be obvious, regardless if combined with Lee or Burg and/or Atkinson.

Examiner would have us believe that the resultant construct of a combination of the three references will be the same construct as presently claimed. It is true that Smith et al disclose using a hydrostatic pressure and frequency of applying the pressure that is substantially the same as used in the present claims. However, he does not combine the hydrostatic pressure with other important conditions that characterize the instant construct and its performance. The perfusion, its rate, oxygen concentration, carbon dioxide concentration and use of the tissue processor for combining all these conditions in one process are not disclosed. For example, a rate of perfusion with a medium according to the invention that results in increase in S-GAG production by as much as 36% cannot be obvious. Examiner's argument that such perfusion is obvious because it provides nutrients for the cells to maintain the cells active for growth does not make sense in view of the obtained results. If that would be as Examiner says, then the higher rate of perfusion providing higher concentration of nutrients should have accounted for higher production of S-GAG. As described above, it is just the opposite, when the perfusion rate is 10 times lower, the production of S-GAG is 36% higher, specifically 107.33 µg/cell construct, then when the rate of perfusion is ten time higher where the S-GAG production is only 78.75 µg cell construct (Table 3). This is a very important aspect particularly as no reference discloses any perfusion rate and its importance for

activation of chondrocytes to produce higher amounts of extracellular macromolecules and increased DNA content. Lee discloses proliferating the cells in a medium containing serum to obtain a sufficient number of cells, and seeding the cells in the construct. Those would be steps performed before the chondrocytes are seeded into the matrix. Lee does not disclose or suggest any activation of cells that would even remotely correspond to the process for producing the instant construct. Burg discloses forming a hydrogel-cell composition for use in forming new tissue where before the cell are incorporated in a construct they can be expanded by culturing in vitro in a medium containing serum. Again, Burg does not disclose or suggest any activation of cells that would even remotely correspond to the process for producing the instant construct and the steps he discloses would be performed before the chondrocytes are seeded into the matrix. Thus neither Smith, Lee or Burg disclose, suggest or even imply formation of the instant construct, importance of the perfusion rate and presence of reduced oxygen concentration for performance of the treated cells according to the invention.

Examiner further dismisses the claimed conditions regarding the oxygen and carbon dioxide concentration. Atmospheric air contains above 20% oxygen. Applicants discovered that when they use decreased (substantially) concentration of oxygen from 20% to 2%, the S-GAG production is approximately 40% higher then when, under the same conditions, the construct is treated at 20% oxygen concentration. In view of these results, Examiner's conclusion that "using slightly less than 20% oxygen would have been an obvious variation that would not be expected to produce a

difference in result" cannot be sustained. As is shown and described in the specification, the lower concentration of oxygen **DOES** make difference and therefore cannot be obvious.

Examiner further argues that Smith et al disclose 7.5% carbon dioxide (col 17, line 10), and using 5% as in claim 94 is an obvious variation that would not be expected to produce a difference in result. Examiner is respectfully asked to note that the use of 7.5% carbon dioxide by Smith refers to release of cartilage cells from the matrix to insure **complete digestion of cartilage** (Col. 17, lines 1-15) in order to isolate the cell. Examiner equals cartilage digestion in the presence of 7.5% of carbon dioxide with a carbon dioxide atmosphere conditions under which the isolated, seeded chondrocytes are activated with hydrostatic pressure, in the decrease oxygen and under perfusion. The use of carbon dioxide for chondrocyte isolation cannot make obvious the use of 5% of carbon dioxide during the process of chondrocytes activation in the tissue processor. One (Smith) is used for isolating cells from the cartilage, the other (instant) is used as one of the conditions for activation of cell withing the matrix together with a complex set of other conditions.

Applicants respectfully submit that the references, in whichever combination, do not provide the same construct as that claimed herein and do not make preparation of such construct obvious. The above listed process conditions resulting in the unique implant construct of the present claims and its functionality are amply described in individual section of the specification outlining the importance for each of these conditions.

Applicants are amazed to find that when nowhere in any of the prior art references there is any mention of importance of the perfusion flow, oxygen or carbon dioxide atmosphere, these can be inherent in the prior art and/or, according to the Examiner, inherently implied from references that never described, suggested or even remotely alluded to them. There is no clairvoyance in the patent law. Either the conditions are important or not. Either they are disclosed or not. Either their use results in substantially different results from those observed and described before in the prior art or not. Instant specification describes importance of these conditions.

The importance of variable flow is disclosed in [0186]-[0189]. Since there was no description of the perfusion flow anywhere in any of these references, such cannot be inherent or implied.

The importance of reduced oxygen and presence of carbon dioxide is described in [0194]-[0196]. Since there was no description of the reduced oxygen requirement anywhere in any of these references, and the normal atmosphere does not contain reduced oxygen, such cannot be inherent or implied. Nor is there 5% carbon dioxide present in the atmosphere.

Importance of the tissue processor is described in [0176]-[0185]. Its use cannot be inherent or implied.

Importance of different types of hydrostatic pressure is described in [0190]-[0193]. Importance of hydrostatic pressure was disclosed by Smith but not the cyclic or constant pressure in conjunction with other conditions.

Determination of exact conditions for production of the instant construct and the resulting construct and its ability to

synthesize S-GAG and DNA in approximately 50% larger amounts is described in [0197]-[0209]. These are not inherent in the processing of combination of cited references. These high yields are a result of the discovery of the conditions to which the construct is subjected during its fabrication.

Applicants respectfully request Examiner to reconsider the rejections of the claims in view of the new claims and these arguments.

SUMMARY

In summary, Claims are amended and arguments are submitted to overcome the prior rejections. It is believed that all claims are in allowable conditions. The notice of allowance is respectfully requested.

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Respectfully submitted,

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